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Original research

Determining the best percent-predicted equation for estimated VO_2 peak by a 1-km moderate perceptually-regulated treadmill walk to predict mortality in outpatients with cardiovascular disease

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ABSTRACT

Objectives: To determine the prognostic ability of established percent-predicted equations of peak oxygen consumption (%PRED) estimated by a moderate submaximal walking test in a large cohort of outpatients with cardiovascular disease (CVD).
Design: Population-based prospective study.
Methods: A total of 1442 male patients aged 25–85 years at baseline, underwent a moderate perceptually-regulated (11–13 on the 6–20 Borg scale) treadmill walk (1k-TWT) for peak oxygen consumption estimation (VO_2 peak). %PRED was derived from ACSM, Ades et al, Morris et al, and the Wasserman/Hansen equations, and their prognostic performance was assessed. Overall mortality was the end point. Participants were divided into quartiles of %PRED, and mortality risk was estimated using a Cox regression model.
Results: During a median 8.2 year follow-up, 167 all-cause deaths occurred. The Wasserman/Hansen equation provided the highest prognostic value. Mortality rate was lower across increasing quartiles of %PRED. Compared to the first quartile, after adjustment for confounders, the mortality risk decreased for the second, third, and fourth quartiles, with HRs of 0.75 (95% CI 0.44–1.29, p = 0.29), 0.67 (95% CI 0.38–1.18, p = 0.17), and 0.37 (95% CI 0.10–0.78, p = 0.009), respectively (p for trend <0.0001). Each 1% increase in %PRED conferred a 4% improvement in survival.
Conclusions: The percent-predicted VO_2 peak determined by Wasserman/Hansen equations applied to the 1k-TWT is inversely and significantly related to survival in cardiac outpatients. The 1k-TWT is a simple and useful tool for stratifying mortality risk in patients participating in secondary prevention programs.

1. Introduction

Peak oxygen consumption (VO_2 peak), determined during maximal incremental cardiopulmonary exercise testing (CPET) is commonly recognized to be the gold standard objective measure of cardiorespiratory fitness (CRF).[1] The determination of VO_2 peak is used for assessing disease severity, predicting prognosis for patients with various pathophysiological conditions including cardiovascular disease (CVD), and to examine the effectiveness of training programs for individuals involved in rehabilitation.[2]

The interpretation of CPET results requires knowledge of a normal response, usually considered with respect to age, gender, body weight, and exercise capacities of healthy volunteers. VO_2 peak is commonly expressed relative to body weight. However, reference values have limitations that involve sample specificity, the exercise protocol, and the presence of disease and medications. Thus, report-

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ing VO_2 peak as a percent-predicted value has been advocated, and several equations to estimate normal VO_2 peak are available.[3,4]

Few investigations have examined the prognostic value of percent-predicted VO_2 peak, over short follow-up, and reported non-univocal conclusions. In patients with severe heart failure, Aaronson and Mancini failed to demonstrate a superior prognostic impact of the percent-predicted VO_2 peak compared with absolute values,[5] while Stelken et al. reported that percent-predicted VO_2 peak was superior to the actual value for predicting mortality in patients with ischemic and dilated cardiomyopathy.[6] More recently, Arena et al. demonstrated that percent-predicted VO_2 peak provided similar or better predictive information compared to the measured value for estimating major cardiac events in a large heart failure cohort.[3]

Little is known regarding the association between submaximal approaches to exercise testing and outcomes in patients with CVD. We have demonstrated that a moderate self-paced 1-km treadmill-walking test (1k-TWT)[7] is useful for predicting survival[8,9] and hospitalization[10] in outpatients with CVD. However, few data are available regarding the application of submaximal tests and the prognostic utility of commonly used peak VO_2 prediction equations.

The aim of the current study was to assess the association between percentage of age-predicted VO_2 peak using the 1k-TWT (%PRED) and all-cause mortality in outpatients with CVD. In addition, we determined the degree to which differences in %PRED might explain variations in survival. This analysis could not only provide insight into risk stratifying patients with CVD but also facilitate discussions between physicians and their patients with regard to physical activity counseling.

2. Methods

The study population consisted of 1442 men (86.6% with coronary heart disease), aged 25–85 years at baseline, referred by their primary care physician to the exercise-based secondary prevention program at the Center for Biomedical Studies Applied to Sport at the University of Ferrara, Italy, between 1998 and 2012. The ultimate goal of the program was promotion and long-term maintenance of a physically active lifestyle in order to improve CRF and functional ability. A home program consisting of 30–60 min of moderate aerobic exercise such as brisk walking, at least 3–4 days and preferably 7 days of the week, was recommended. All patients were also encouraged to improve physical activity habits by increasing daily activities, such as walking breaks at work, gardening, or household work.

Patients included in the study were medically stable, with symptoms and therapy that have remained unchanged for at least three months before testing. Subjects with heart failure classified as New York Heart Association class II or higher, and those who had conditions that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were excluded.

Left ventricular ejection fraction derived from prior echocardiographic evaluations, and standard blood chemistry analyses previously performed were registered. Before admission to the program, participants underwent a comprehensive clinical evaluation, including medical history. Weight and height were measured and used to calculate body mass index (BMI). Blood pressure (BP) was measured, and hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or use of antihypertensive agents. The study was approved by the Ethics Committee of the University of Ferrara, no. 22–13, and all participants gave written informed consent.

VO_2 peak was estimated for each participant at the time of their baseline examination using the 1k-TWT.[6] The test was carried out as follows: the patients were instructed to select a pace that they could maintain for 10 to 20 min at a moderate perceived exercise intensity using the Borg 6–20 scale. Patients began the test walking on the level at a walking speed of 2.0 km h^{-1}, with subsequent increases of 0.3 km h^{-1} every thirty seconds up to a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale. The 1k-TWT then started and the Rate of Perceived Exertion (RPE) was assessed every two minutes, adjusting walking speed to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). The equation for VO_2 peak estimation was then applied considering age, BMI, HR and time to complete the 1 k-TWT.[6] Patients unable to complete the 1k-TWT at walking speed $\geq$ 3.0 km/h were considered at very poor cardiorespiratory fitness and excluded from the analysis.

Percent-predicted VO_2 peak values were calculated according to normative values as proposed by Wasserman and Hansen,[11] Ades et al.[12] Morris et al.[13] and ACSM.[14]

Participants were followed for all-cause mortality from the date of their baseline examination for up to 10 years. Patients were flagged by the regional Health Service Registry of the Emilia-Romagna region, who provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status. Time from initial evaluation to death was calculated in months. The prognostic significance of %PRED values derived from the above mentioned equations were assessed.

Statistical analyses were performed using MedCalc 16.2.1 software, Mariakerke, Belgium. The participants were divided into quartiles on the basis of the %PRED values by each of the equations considered. One way ANOVA was used to determine differences between quartiles in terms of age, BMI, left ventricular ejection fraction, total and HDL cholesterol, triglycerides, glycaemia and absolute estimated VO_2 peak. Differences in categorical variables were assessed using the χ^2 test for trend. Overall mortality was used as the end point for survival analysis. Differences in survival across quartiles during the follow up period were assessed using Kaplan–Meier curves. Cox proportional hazard models were employed to determine the multivariable adjusted relative risk of mortality across quartiles. Demographics and clinical characteristics significantly associated with %PRED VO_2 peak were included in the multivariable Cox regression model as potential confounders. Individuals in the lowest %PRED VO_2 peak quartile were considered the reference group in the regression model. To assess the discriminatory accuracy of percent-predicted VO_2 peak in estimating survival, receiver-operating-characteristic (ROC) curves were constructed and the corresponding areas under the curve were calculated. The level of statistical significance was set at $p < 0.05$.

3. Results

A total of 1442 patients were referred to our Center. 186 participants were unable to complete the 1k-TWT at walking speed $\geq$ 3.0 km/h, and were excluded from the analysis. The clinical characteristics of the 1256 patients included in the analysis are presented in Table 1. Average walking speed during 1k-TWT was 4.4 ± 1.1 km h^{-1}. Mean heart rate was 95 ± 14 beat min^{-1}, representing $60\% \pm 6\%$ of the age-predicted maximal heart rate (based on 220-age). VO_2 peak values predicted from 1k-TWT were 23.9 ± 4.6 ml $kg\ min^{-1}$.

During the median follow-up period of 8.2 years (interquartile range 6.1–10), there were 167 deaths from any cause with an average annual mortality of 1.3%. Patients who died compared to those who survived at the baseline examination were significantly older, had a lower left ventricular ejection fraction (LVEF), had a higher serum creatinine, a higher prevalence of Coronary Artery Bypass Graft (CABG) and Percutaneous Transluminal Coronary Angioplasty (PTCA), a higher use of diuretics, and a lower use of statins (Table 1).

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